Delegates Book

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Title: CLINICAL TRIALS AND FURTHER IMPROVEMENTS OF PRODRUG ACTIVATION GENE THERAPY WITH *E. COLI* NITROREDUCTASE

Background/aims: *E. coli* nitroreductase (NTR) can reduce the prodrug 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB1954) to cytotoxic, DNA-crosslinking derivatives. Clinical trials in primary or secondary liver cancer and prostate cancer were designed to determine safety; level and distribution of adenovirus-mediated NTR expression; and evidence of tumouricidal activity when combined with CB1954. Parallel laboratory studies aimed to investigate the benefit of a conditionally replicating adenovirus (CRAd) vector, and to improve the catalytic activity of NTR with CB1954.
Methods: Trials involved local injection of the CTL102 virus under ultrasound guidance. Operable tumours were resected after 1 – 9 days. Patients with inoperable cancers received intravenous CB1954, 2 days after virus. An E1B55K-deleted CRAd was compared with CTL102 for NTR expression and tumouricidal activity with CB1954, *in vitro* and in mice. Improved NTR mutants were generated by site-directed mutagenesis based on the crystal structure.
Results: CTL102 was safe at all doses ($\leq 5 \times 10^{11}$ particles), and gave increasing level and distribution of NTR expression as the dose was escalated. Instances of stable disease, and post-treatment declines in AFP or PSA are suggestive of tumouricidal activity. CRAd-NTR showed higher NTR expression and greater efficacy with CB1954 *in vitro* than a 20x higher MOI of CTL102, and CRAd-NTR+CB1954 also showed the greatest reduction in growth of SW480 tumours in nude mice. 50 NTR mutants showed greater sensitisation of *E. coli* to CB1954 than WT, and several of these have been tested in human tumour cells. The F124K mutant is ~5-fold more efficient than WT in sensitising cells to CB1954.
Conclusion: Initial results of ongoing clinical trials of CTL102+CB1954 are encouraging. In the laboratory, CRAd vectors, and catalytically improved "*turbo*-NTR", each improve the efficacy of prodrug activation gene therapy with CB1954. These data all support the rationale for a future clinical trial of CRAd-*turbo*-NTR with CB1954.

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